Hereditary tyrosinaemia

Clinical, enzymatic, and pathological study of an infant with the acute form of the disease

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Hereditary tyrosinaemia, a rare metabolic disorder with its onset in infancy or early childhood, was first described by Baber (1956) and linked with an abnormality in tyrosine metabolism in 1957 (Sakai and Kitagawa, 1957a, b). It presents clinically in two forms.

Firstly, an acute form with symptoms occurring within a few weeks or months of birth and characterized by rapidly progressive cirrhosis, bleeding diathesis, hypoglycaemia, and renal tubular dysfunction. In addition there is a generalized amino-acidaemia with especially high concentrations of tyrosine and methionine accompanied by an overflow aminoaciduria. Death invariably ensues from liver failure associated with infection or bleeding, or both, within the first year of life.

Secondly, a subacute or chronic form of the disease in which the initial symptoms are generally manifest before 12 months of age. This form is more common, and affected infants present with failure to thrive, gastrointestinal symptoms, hepatic cirrhosis, and multiple renal tubular defects associated with secondary rachitic changes. The amino acid abnormality is usually confined to tyrosine, but there may be a rise in methionine in the terminal phase of the disease. Death usually occurs within the first decade.

Both forms of the disorder seem to be inherited as autosomal recessive traits (Gentz, Jagenburg, and Zetterström, 1965). Opinions on the nature of the primary defect differ. The defect in tyrosine metabolism is due to reduced activity of the tyrosine hydroxylating enzyme p-hydroxyphenylpyruvate oxidase (pHPPA oxidase) (La Du and Gjessing, 1972), and some authors have claimed that this represents the primary defect with the abnormality in methionine metabolism occurring secondary to the severe liver dysfunction (Gentz et al., 1965: Halvorsen et al., 1966). However, Perry et al. (1965) believe that the defect in methionine is the primary one and that the disturbance in tyrosine metabolism
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is secondary. A third hypothesis is that the primary defect is neither tyrosine nor methionine metab-
olism and is as yet unrecognized (Woolf, 1966; 
Gaul et al., 1970; La Du and Giessing, 1972).

This report describes the case of a young infant 
who presented with the acute fulminating type of 
hereditary tyrosinaemia and in whom dietary treat-
ment was unsuccessful. The death of the infant 
enabled a wide range of hepatic enzymes, not so 
far studied in any one patient, to be assayed and a 
detailed necropsy study to be made.

Case report

The patient, a 7-week-old boy, was born at term with 
a birthweight of 3118 g and fed on cow’s milk with cane 
sugar. At about 3 weeks of age his mother noticed an 
unpleasant sweetish smell from his motions and body 
similar to that in a sib who had died, aged 2 months, a 
few years previously with a liver disease. Jaundice 
became apparent at 6 weeks. At 7 weeks he developed 
a high temperature and bruising was noted over his 
right thigh and later over his lower abdomen. He 
was admitted to hospital.

On admission he weighed 4660 g. He was slightly 
jaundiced and very irritable with a temperature of 
38.3 °C, and a very pronounced, unpleasant sweet smell, 
similar to rotten cabbage, was noted from his body. 
Respirations were 38/min and shallow. The liver was 
2 fingerbreadths below the costal margin and of firm 
consistency. The spleen was not enlarged and there 
was no evidence of ascites. An umbilical hernia was 
present and some craniothubes was noted. Bruising 
and swelling were present across the lower abdomen and 
right thigh. He had a grossly purulent nasal discharge 
and over the next 24 hours respiratory distress was more 
pronounced. He was treated initially with intravenous 
glucose and ampicillin and cloxacinil. Because the 
findings at the necropsy of his sister had suggested the 
disorder described by Perry et al. (1965) as hyper-
methioninaemia he was started on a low methionine diet 
two days after admission. There were 3 healthy sibs in 
his family and a history of possible consangunuity 
five generations before.

Investigations. Chest x-ray examination showed 
irregular collapse of the basal segments of the left lower 
lobe with two further subsegmental areas of collapse 
around the left hilum. There was no skeletal abnor-
mality. Coagulation activity was less than 1%. Plasma 
fibrinogen was 1·0 g/l, the Fibrindex test was slightly 
prolonged, and no circulating anticogulant was noted. 
Hb was 12·1 g/dl and the white cell count was 22 \times 10^9/l (22 000/mm³). Biochemical findings before treat-
ment were as follows: serum bilirubin 177 μmol/l 
(10 mg/100 ml), alkaline phosphatase 533 KA-U/l, 
aspartate aminotransferase 156 units/l, glucose 1·4 
mmol/l (25 mg/100 ml), albumin 35·0 g/l (3·5 g/100 
ml), total protein 50·0 g/l (5·0 g/100 ml), and urea 1·7 
mmol/l (10·2 mg/100 ml). Sodium, potassium, chloride, 
bicarbonate, cholesterol, calcium, inorganic phosphate, 
urate, ammonia, and lactate dehydrogenase levels were 
normal. The amino acid levels in the plasma, cerebro-
spinal fluid (CSF), and urine are shown in Tables I and II. 
In a generalized aminoacidaemia the most pronounced 
rises were in methionine concentration followed by 
tyrosine, ornithine, arginine, phenylalanine, lysine, 
proline, and threonine in that order. Amino acid 
levels in the CSF were also generally raised, mostly so 
in taurine, glutamine, methionine, tyrosine, and histi-
dine. An overflow type of generalized aminoaciduria 
was present and tyrosyl metabolites, p-hydroxyphenyl-
pyruvic acid (pHPAA), and p-hydroxyphenylacetic acid 
(pHPAA) were present in high concentration in the 
urine. No p-hydroxyphenylpyruvic acid (pHPAA) 
was noted but this may have been due to delay in testing 
for this substance. Mellituria was present with fructose, 
galactose, and sucrose identified chromatographically. 
The amino acids were estimated by ion exchange 
chromatography using a Standard Technicon Amino-
Acid Analyser.

Dietary treatment. The initial diagnosis was 
made in the Regional Hospital, Galway, and treatment 
with a low methionine diet instituted two days after 
admission at the age of 8 weeks. One week later the 
infant was transferred to the Royal Belfast Hospital for 
Sick Children, where facilities were available for moni-
toring this type of treatment. The low methionine diet 
was continued and phenylalanine and tyrosine were 
also restricted. A special amino acid mixture was 
prepared* which contained no methionine, phenylala-
nine, or tyrosine. A restricted quantity of these amino 
acids was given as cows’ milk, which supplied about 
50 mg/kg of phenylalanine and of tyrosine, and 20 mg/ 
kg of methionine. The carbohydrate was in the form of 
a polyglucose polymer (Caloreen*) and the essential 
fat given as Prospanol† (50% arachis oil in water). On 
restricting the methionine intake the peculiar smell, 
notably lessened. However, despite the special diet, 
the baby’s condition deteriorated, the abdomen became 
distended, respiratory distress increased, and the 
temperature rose to 38·2 °C. Jaundice did not increase 
and was never severe at any stage of the illness. He 
died aged 9½ weeks with terminal pneumonia and liver 
failure. A special diet had been given for a total of 
11 days, the low methionine diet being given for 6 days, 
and a low methionine, phenylalanine, tyrosine diet for 
the last 5 days. The diet resulted in a dramatic decrease 
in the urinary excretion of amino acids, tyrosyl met-
obolites, and disappearance of urinary sugars. On the 
low methionine diet a general reduction was noted in 
plasma amino acid levels with the exception of threo-
nine, glycine, alanine, cystine, phenylalanine, and 
histidine, which rose. The tyrosine level remained 
unchanged. After a further 5 days on the low methio-
nine, phenylalanine, tyrosine diet the level of all plasma 
amino acids fell, that of the branched chain amino 
acids valine, leucine, and isoleucine substantially.

*Scientific Hospital Supplies Ltd., Liverpool.
**Hepatic enzyme studies.** The liver was removed within one hour of the patient’s death and immediately stored at -20 °C. Control livers were obtained from ‘cot death’ infants with no obvious lesion found at necropsy and stored at -20°C within three to six hours of death. The results of the hepatic enzyme assays carried out on the patient and on the controls are shown in Tables III-V. Three main groups of enzymes were studied; general liver enzymes, including those with cytoplasmic, lysosomal, microsomal, and mitochondrial location (Table III); specific enzymes of the tyrosine, methionine, and lysine pathway (Table IV); and specific enzymes involved in fructose and galactose metabolism (Table V).*

Among the general liver enzymes assayed (Table III) the activities of the patient’s aspartate aminotransferase, lactate dehydrogenase, and isocitrate dehydrogenase were similar to those of the controls. There was a striking reduction in alanine aminotransferase activity, which was confirmed in three different liver homogenate preparations. The activities of the alkaline phosphatase, acid phosphatase, and cholinesterase enzymes were greater than those of the controls, the alkaline phosphatase activity particularly being raised. In general, the specific enzymes studied in the patient had a lower level of activity than the control samples (Tables IV and V). There was deficient activity of the tyrosine pathway enzyme, pHPPA oxidase, the trans-sulphuration enzymes cystathionine synthase and cystathionase, of lysine oxoglutarate reductase, and of the fructose-1-P and fructose-1,6 diP aldolases. Only tyrosine-L-oxoglutarate aminotransferase, the lysine pathway enzyme saccharopine dehydrogenase, and galactose-1-P uridyl transferase activities lay within the control range.

**Pathology.** Necropsy was performed within one hour of death. All internal organs were examined grossly and microscopically. Only those organs that showed pathological changes are reported on here.

The baby weighed only 3500 g and had a crown-heel length of 55 cm. There was mild icterus and generalized subcutaneous oedema. The only external abnormality was a small umbilical hernia.

**Lungs.** Terminal bronchopneumonia.

**Liver.** Weight 175 g. The parenchyma was deeply bile-stained with no apparent nodularity. The gallbladder communicated with a patent biliary duct system. Histology of the liver showed the normal architecture completely disrupted, owing to an unusual grouping of hepatocytes, into small and irregularly shaped acinar formations, some of which had central lumens (Fig.). These lay embedded in a diffuse fibrous stroma infiltrated by occasional lymphocytes,
TABLE II
Amino acid levels in urine of patient with acute tyrosinaemia and in controls

<table>
<thead>
<tr>
<th>Urine levels (μmol/mg creatinine)</th>
<th>On admission</th>
<th>After 4 days</th>
<th>Control</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taurine</td>
<td>0.57</td>
<td>Trace</td>
<td>3.45</td>
<td>0.6</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>0.35</td>
<td>—</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>Hydroxyproline</td>
<td>7.7</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Threonine</td>
<td>110.0</td>
<td>27.8</td>
<td>0.58</td>
<td>0.54</td>
</tr>
<tr>
<td>Glutamine</td>
<td>46.2</td>
<td>12.7</td>
<td>1.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Serine</td>
<td>119.1</td>
<td>3.0</td>
<td>1.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>1.1</td>
<td>34.0</td>
<td>0.04</td>
<td>0.21</td>
</tr>
<tr>
<td>Proline</td>
<td>0.75</td>
<td>—</td>
<td>0.04</td>
<td>0.21</td>
</tr>
<tr>
<td>Glycine</td>
<td>107.5</td>
<td>13.0</td>
<td>2.60</td>
<td>2.79</td>
</tr>
<tr>
<td>Alanine</td>
<td>38.7</td>
<td>11.2</td>
<td>1.06</td>
<td>1.37</td>
</tr>
<tr>
<td>Valine</td>
<td>2.40</td>
<td>—</td>
<td>0.02</td>
<td>0.27</td>
</tr>
<tr>
<td>Cystine</td>
<td>3.5</td>
<td>—</td>
<td>0.22</td>
<td>0.22</td>
</tr>
<tr>
<td>Methionine</td>
<td>1.5</td>
<td>—</td>
<td>—</td>
<td>0.28</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.16</td>
</tr>
<tr>
<td>Leucine</td>
<td>1.48</td>
<td>—</td>
<td>—</td>
<td>0.20</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>10.2</td>
<td>4.1</td>
<td>0.24</td>
<td>0.37</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>37.0</td>
<td>1.1</td>
<td>0.16</td>
<td>—</td>
</tr>
<tr>
<td>Ornithine</td>
<td>21.0</td>
<td>9.9</td>
<td>—</td>
<td>0.12</td>
</tr>
<tr>
<td>Lysine</td>
<td>67.0</td>
<td>58.7</td>
<td>0.36</td>
<td>0.58</td>
</tr>
<tr>
<td>Arginine</td>
<td>7.4</td>
<td>1.4</td>
<td>0.62</td>
<td>0.10</td>
</tr>
<tr>
<td>Methionine sulphoxide</td>
<td>0.80</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Histidine</td>
<td>74.4</td>
<td>22.0</td>
<td>1.82</td>
<td>1.28</td>
</tr>
<tr>
<td>Homocystine</td>
<td>—</td>
<td>22</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cystathionine</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ethanolamine</td>
<td>—</td>
<td>—</td>
<td>0.62</td>
<td>0.44</td>
</tr>
</tbody>
</table>

TABLE III
General liver enzyme activity in patient with acute tyrosinaemia and in normal control infants

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Patient (age 94 w)</th>
<th>Infant controls aged</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 d</td>
<td>3 w</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>643</td>
<td>600</td>
</tr>
<tr>
<td>(nmol/min per mg protein)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>25</td>
<td>259</td>
</tr>
<tr>
<td>(nmol/min per mg protein)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>1607</td>
<td>1255</td>
</tr>
<tr>
<td>(nmol/min per mg protein)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isocitrate dehydrogenase</td>
<td>283</td>
<td>203</td>
</tr>
<tr>
<td>(nmol/min per mg protein)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>69.1</td>
<td>14.0</td>
</tr>
<tr>
<td>(nmol/min per mg protein)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acid phosphatase</td>
<td>69.0</td>
<td>34.3</td>
</tr>
<tr>
<td>(nmol/min per mg protein)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholinesterase</td>
<td>1.47</td>
<td>0.72</td>
</tr>
<tr>
<td>(units/min per mg protein)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

neutrophils, and eosinophils. One section included a solitary regenerative micronodule composed of hepatocytes with small intracytoplasmic fat droplets. Elsewhere fatty change was not a feature and no excess glycogen was demonstrable. Bile and haemosiderin pigments were prominent in most of the hepatocytes and numerous bile thrombi blocked the canaliculi. The portal tracts showed no excess of fibrous tissue and there was no bile duct proliferation. Pancreas. Weighed 16 g. In several sections there was a pronounced increase in the number of islets as compared with age-matched controls. Several islets were unusually large. Within each islet the normal relative proportions and distribution of α, β, and δ cells appeared to be maintained (Gomori acid fuchsin stain). No increased mitotic activity or degenerative changes were seen in any of the islets. The exocrine system appeared normal.
TABLE IV

Activity of enzymes of tyrosine, methionine, and lysine pathways in patient with acute tyrosinaemia and in normal infants and adult controls

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Patient (age 9½ w)</th>
<th>Infant controls aged</th>
<th>Adult controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 d</td>
<td>3 w</td>
<td>4 w</td>
</tr>
<tr>
<td>pHPPA oxidase (mmol/min per mg protein)</td>
<td>0·9</td>
<td>5·8</td>
<td>19·0</td>
</tr>
<tr>
<td>Tyrosine-L-oxoglutarate aminotransferase (mmol/min per mg protein)</td>
<td>62·3</td>
<td>46·6</td>
<td>23·0</td>
</tr>
<tr>
<td>Cystathionine synthase (mmol/hour per mg protein)</td>
<td>7·2</td>
<td>10·1</td>
<td>37·2</td>
</tr>
<tr>
<td>Cystathionase (mmol/hour per mg protein)</td>
<td>3·9</td>
<td>18·5</td>
<td>17·5</td>
</tr>
<tr>
<td>Lysine oxoglutarate reductase (mmol/hour per mg protein)</td>
<td>73</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Saccharopine dehydrogenase (mmol/hour per mg protein)</td>
<td>79</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

TABLE V

Activity of enzymes of fructose and galactose pathway in patient with acute tyrosinaemia, in control infants, and galactosaemic infants

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Patient (9½ w)</th>
<th>Infant controls aged</th>
<th>Galactosaemic infant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4 w</td>
<td>5 w</td>
</tr>
<tr>
<td>Fructose-1-6-diP aldolase (umol/hour per mg protein)</td>
<td>0·9</td>
<td>3·2</td>
<td>3·7</td>
</tr>
<tr>
<td>Fructose-1-P aldolase (units/mg protein)</td>
<td>0·8</td>
<td>3·7</td>
<td>3·7</td>
</tr>
<tr>
<td>Galactose-1-P-uridytransferase (nmol/min per mg protein)</td>
<td>4·9</td>
<td>5·1</td>
<td>2·0</td>
</tr>
</tbody>
</table>

Kidneys. Right, weighed 45 g, left, 50 g. Each was swollen, showing cortical pallor and an increased corticomedullary ratio of 1:2. Renal vessels were patent. Histological examination showed mild variability in size of the glomeruli but they were normocellular with no basement membrane thickening. The juxtaglomerular apparatus was not hyperplastic and there was no excess granularity. The tubular epithelium in all zones was intensely eosinophilic and granular. Tubular dilatation was only of moderate severity and confined mainly to the proximal convoluted segments. Small round amorphous globules were present within these and may have been proteinaceous in nature.

Discussion

There are many reasons for the presence of increased plasma and urinary tyrosine levels accompanied by the excretion of tyrosyl metabolites. In the differential diagnosis of so-called 'acute hereditary tyrosinaemia' only those diseases presenting within the first year of life associated with hepatorenal dysfunction need be considered.

Nonhereditary tyrosinaemia and methioninaemia have been described in acute and chronic liver disease associated with cirrhosis (Levine and Conn, 1967) and with neonatal hepatitis (Carpenter, 1968; Yu, Walker-Smith, and Burnard, 1971). Here the levels of tyrosine and methionine revert to normal with recovery of hepatic function. In the hepatic form of glycogen storage disease (von Gierke's Disease) the diagnosis is established by finding an increase in tissue glycogen content together with a marked deficiency of hepatic glucose-6-phosphatase activity (Howell, 1972). Increased activity of this enzyme has been reported in a patient with hereditary tyrosinaemia (Silverberg, 1967).

The distinguishing feature in classical galactosaemia is the absence of galactose-1-P-uridytransferase in red blood cells and in hepatic tissue. The microscopic appearance of the liver may show a striking similarity to that found in acute tyrosinaemia. Normal activity of red cell galactose-1-P-uridytransferase has been reported in patients with hereditary tyrosinaemia (Gaull et al., 1970; Halvorsen et al., 1966) and in the present study.

The disorder most likely to be confused with the
order fructosuria

Both have acute form and improvement of fructosuria when appearance show. Clinically saemia. (0 P-aldolase aemia and has been reduction in fructose-1-6 saemia (Odi6vre, Gautier, and Rieu, 1969). However, severe deficiency in the activity of hepatic fructose-1-P-aldolase (0 to 12% of normal) with a less severe reduction in fructose-1-6 diP-aldolase activity (approximately 25%, of normal) (Froesch, 1972). In the patient with hereditary tyrosinaemia reported here a moderate decrease in the activity of both these enzymes has been found. Recently the activity of fructose-1, 6-diphosphatase has been reported as deficient in patients with the clinical and biochemical features of the classical form of hereditary fructosuria (Bakker et al., 1974; Baerlocher et al., 1971; Hülsmann and Fernandes, 1971).

Treatment. In the acute type of hereditary tyrosinaemia the results of dietary therapy have been largely unsuccessful, even when the diet has been started within the first month of life, and most infants die within the first year (Larochelle et al., 1967; Bodegard et al., 1969). The diet in our patient was started at the age of 8 weeks. A dramatic improvement in the renal tubule handling of amino acids resulted, but the effect on the plasma amino acid abnormalities and the clinical state was disappointing. A temporary form of the disease has been described (Gaull et al., 1970; Harries et al., 1969; Pickering and Bower, 1972) in 3 infants in whom liver function and the amino acid abnormalities reverted to normal after some months of dietary treatment and continued so on a normal diet. A low phenylalanine, tyrosine, and methionine diet would therefore seem profitable in all cases of acute tyrosinaemia.

Pathology. Renal tubular dilatation, pancreatic islet hyperplasia, and a peculiar diffuse hepatic fibrosis with pseudocinar groupings of hepatocytes form the triad of histopathological features seen in most cases of hereditary tyrosinaemia. They were present in our case, but the spongiform degeneration of the brain which has been described was not demonstrable in several routine brain sections. Neither was there any gross or histological evidence of rickets, but its development seems to be age-dependent, occurring in children who survive longer. Jevtic, Thorp, and Hruban (1974) thought that hypertrophy and hyperplasia of the juxta-
glomerular apparatus might be a specific diagnostic feature of hereditary tyrosinaemia. Special staining of the juxtaglomerular granules in our case showed no morphological evidence of this. The same authors record a variability in glomerular size and glomerular basement membrane thickening. Glomerular size varied slightly in our patient but was within the normal range and, in our view, was explicable by the different planes of section through the glomerular tufts. No basement membrane thickening was present.

**Hepatic enzymes.** It was hoped that the study of the hepatic enzymes would throw some light on the basic defect in this disorder. In the general group alanine aminotransferase activity was notably deficient while that of aspartate aminotransferase was within the normal range. The time lag in performing this enzyme estimation was the same as that of the controls, and co-incubation studies failed to detect the presence of a specific diffusible inhibitor to the enzyme. Alanine aminotransferase is 90% cytoplasmic in origin while that of aspartate aminotransferase is 40% mitochondrial and 60% cytoplasmic. However, since both lactate dehydrogenase and isocitrate dehydrogenase are also cytoplasmic in origin and showed normal activity it seems that the marked decrease in alanine aminotransferase was not due solely to cytoplasmic leakage. Decrease in the activity of this enzyme has been reported in different forms of liver dysfunction (McLean, 1966; Sommerville et al., 1960; Zelman, Wang, and Appelhanz, 1959).

In keeping with other reports (La Du and Gjessing, 1972), activity of the cytoplasmic enzyme pHPPA oxidase was decreased in our case, whereas that of tyrosine aminotransferase was within the control range. The activity of this latter enzyme in patients with hereditary tyrosinaemia has variously been reported to be greatly deficient to normal (Gentz et al., 1965; La Du and Gjessing, 1972). It is present in both cytoplasm and mitochondria. The activity of both the enzymes of the trans-sulphuration pathway was below those of the control range. Diminished activity of the methionine-activating enzyme cystathionine synthase and cystathionase have previously been reported (Gaul et al., 1970; Perry, 1967) in patients with hereditary tyrosinaemia. The reduced activity of the methionine-activating enzyme is thought to account for the high methionine levels. Of the two lysine enzymes studied the activity of lysine oxoglutarate reductase was substantially decreased, while that of saccharopine dehydrogenase was similar to one of the two adult controls. Galactose-1-P-uridyl transferase activities lay within the normal range, but the activity of both fructose-1-6-diphosphate aldolase and fructose-1-P aldolase was reduced to 25% of the control livers. The determination of the activity of these three enzymes is important in the differential diagnosis of the acute form of tyrosinaemia, and finding reduced activity of fructose aldolase enzymes may make the distinction between fructosaemia and tyrosinaemia even more difficult.

**Conclusion**

Our findings do little to further knowledge of the basic defect in acute tyrosinaemia of infancy. The most that can be said is that, from whatever cause, the activity of many of the specific hepatic enzymes is reduced, and this supports the hypothesis that the primary defect is of neither tyrosine nor methionine metabolism.

**References**

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Hereditary tyrosinaemia


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Hereditary tyrosinaemia. Clinical, enzymatic, and pathological study of an infant with the acute form of the disease.

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